BIRTH DEFECT RISK FACTOR SERIES: DOWN SYNDROME

DEFINITION

Down syndrome is the most common autosomal abnormality among live births. Most Down syndrome cases result from total trisomy 21, with trisomy 21 mosaicism and translocations involving chromosome 21, each accounting for less than 5 percent of the diagnoses (Stoll et al., 1998; Bishop et al., 1997; Stoll et al., 1990; Baird and Sadovnic, 1988; Iselius and Lindsten, 1986; Leisti et al., 1985; Owens et al., 1983). The prenatal prevalence of Down syndrome is much higher than among live births, with only approximately 70% of fetuses with Down syndrome identified at mid-trimester surviving to term (Hook, 1983). It has been estimated that trisomy 21 occurs on 0.45% of concepti and that 76.2% of these do not survive to term (Hassold and Jacobs, 1984). Down syndrome is associated with a variety of structural malformations, particularly cardiac malformations (Torfs and Christianson, 1998; Kallen et al., 1996).

Over the last several decades, women carrying a fetus with Down syndrome have been found to have low maternal serum levels of alpha-fetoprotein and estriol and elevated levels of human chorionic gonadotropin (Canick and Saller, 1993). Prenatal screening of these substances, along with chorionic villus sampling and amniocentesis, have allowed Down syndrome to be identified in utero. Studies from various birth defects surveillance systems have found that, in regions where elective termination is allowed, the birth prevalence of Down syndrome is reduced (Chaabouni et al, 2001; De Vigan et al., 2001; Verloes et al., 2001; Forrester et al., 1999; Mansfield et al., 1999; Riley et al., 1998; Stoll and EUROCAT Working Group, 1995; Stoll et al., 1994; Stoll et al., 1990).

ETIOLOGY

Down syndrome involving total trisomy 21 results from nondisjunction, usually in formation of the eggs or sperm, where a gamete ends up with an extra chromosome 21. Nondisjunction may occur in the first meiotic stage (MI) or the second meiotic stage (MII).

The extra chromosome 21 is of maternal origin in 80-93 percent of the cases and of paternal origin in 7-20 percent of the cases. Among trisomy 21 cases of maternal origin, approximately 75 percent result from nondisjunction in MI and 25 percent in MII while 40 percent of trisomy 21 cases of paternal origin occur from nondisjunction in MI and 60 percent from nondisjunction in MII (Jyothy et al., 2001; Muller et al., 2000; Antonarakis, 1998; Savage et al., 1998; Yoon et al., 1996; Antonarakis et al., 1992; Buraczynska et al., 1989; Mattei et al., 1979; Magenis et al., 1977). There is no maternal age difference between maternal MI and MII nondisjunction (Antonarakis, 1993; Sherman et al., 1994). One investigation observed higher paternal age with paternal MI than MII nondisjunction (Petersen et al., 1993) although no paternal age difference was reported in another study (Savage et al., 1998); however, these studies were based on small numbers of cases. One investigation noted that a higher proportion of males than females occurred from paternal MII nondisjunction (Savage et al. et al., 1998).

DEMOGRAPHIC FACTORS

The only well established risk factor for Down syndrome is **advanced maternal age** (Hecht and Hook, 1996; Mikkelsen, 1985). Age-specific rates have been well documented (Hecht and Hook, 1996). One study found that women who had a **reduced ovarian complement** (congenital absence or removal of an ovary) were at increased risk of having an infant with Down syndrome. This may suggest that the increased risk of Down syndrome with increased maternal age may be related to the physiological status of the ovaries or the eggs (Freeman et al., 2000; Hassold and Jacobs, 1984). Other potential explanations for the association between Down syndrome risk and advanced maternal age include delayed fertilization, changing hormone levels, and “relaxed selection” (Hassold and Jacobs, 1984).

In a few studies, **advanced paternal age** (>49 years) has been associated with increased risk of Down syndrome births (McIntosh et al., 1995; Murdock et al., 1984; Erickson and Bjerkedal, 1981; Stene et al., 1979). The risk for advanced paternal age has not been large, and is considerably diminished with the appropriate adjustment for maternal age. A large number of studies have failed to find evidence of this effect (Stoll et al., 1990; Janerich and Bracken, 1986; Roth et al., 1983).

An association has been found between risk of Down syndrome and **age of the maternal grandmother at the mother’s birth** (Mikkelsen, 1985; Aagesen et al., 1984). Female meiosis starts in fetal life, and nondisjunction in the first meiotic division of a female might be induced during the fetal period, especially if her mother is older.

Several studies have reported **secular trends** in Down syndrome prevalence; however, these trends have not been consistent, with some studies reporting an increase while other a decline (O’Leary et al., 1996; CDC, 1994; Hahn and Shaw, 1993; Evers-Kiebooms et al., 1989; Baird and Sadovnic, 1988; Iselius and Lindsten, 1986; Leisti et al., 1985; Owens et al., 1983; Adams et al., 1981; Hook and Cross, 1981; Harlap, 1974).

Down syndrome prevalence is known to vary by **race/ethnicity**. Hispanic infants exhibit higher rates of Down syndrome than other infants, even after differences in maternal age was considered (CDC, 1994). Another investigation also found Down syndrome rates to be highest in Hispanics, followed by Asians, whites, Native Americans, and African-Americans (Chavez et al., 1988). One study reported increased risk of Down syndrome among offspring of Vietnamese mothers when compared with offspring of non-Hispanic white mothers in Californoa (Shaw et al., 2002). Racial/ethnic differences in Down syndrome rates may be due partly to differential use of prenatal diagnosis services. Racial composition of women who use prenatal screening services varied from the racial composition of the U.S. population (Meaney et al., 1993), though racial difference in usage was not found in another study (Naber et al., 1987). Also, use of prenatal diagnostic services and abortion significantly reduced the birth prevalence of Down syndrome among white women but not among women of other races in Atlanta (Krivchenia et al., 1993). That was not supported in a Los Angeles study (Wilson et al., 1992). Racial differences may also reflect differential underdiagnosis of the defect at birth.

Down syndrome prevalence varies by **sex**. Among live births, males have higher Down syndrome rates than females, although the discrepancy is less severe among fetuses, suggesting differential in-utero survival between the sexes (Lary and Paulozzi, 2001; Riley et al., 1998; Bishop et al., 1997; Huether et al., 1996; Kallen et al., 1996; Mikkelsen, 1992; Stoll et al., 1990; Bell, 1989; Iselius and Lindsten, 1986; Leisti et al., 1985). Down syndrome is also associated with lower **birth weight**, **prematurity**, and **intrauterine growth retardation** but not **plurality** (Lapunzina et al., 2002; Rasmussen et al., 2001; Riley et al., 1998; Doyle et al., 1991; Ramos-Arroyo et al., 1991; Khoury et al., 1988; Kallen, 1986).

One investigation failed to identify any association between Down syndrome and **altitude** (Castilla et al., 1999).

REPRODUCTIVE FACTORS

An association of Down syndrome with **multiparity** (Schimmel et al., 1994) tends to disappear when maternal age is taken into account (Chan et al., 1998; Castilla and Paz, 1994; Haddow and Palomaki, 1994).

First born infants may be at higher risk of Down syndrome than are those later born, independent of maternal age (Hay and Barbano, 1972). However, this is a very small effect if it exists (Janerich and Bracken, 1986), and another investigation reported firstborns to be at lower risk of Down syndrome (Stoll et al., 1990).

A cluster investigation (Brender, 1986) implicated **short pregnancy interval** as a risk factor. Other reports had noted that **periods of anovulatory activity followed by conception** appear to correlate with increased occurrence of Down syndrome (Jongbloet et al., 1982; Jongbloet and Vrieze, 1985). It is possible that conceptions occurring during the transitional period between anovulation and the establishment of regular ovulation after childbirth might be more vulnerable to maternal meiotic nondisjunction. Therefore, a short interpregnancy interval might possibly increase a woman's risk of subsequently bearing a Down syndrome child.

That theory has also been posed as an explanation for the observation that risk of Down syndrome is associated with **season of child's conception or delivery** and **season of mother's conception** (Jongbloet, 1994; Videbech and Nielsen, 1984; Jongbloet et al., 1982; Rothman and Fabia, 1976; Harlap, 1974). However, other investigations failed to identify **seasonal variation** in month of last menstrual period or date of delivery for Down syndrome cases (Castilla et al., 1990; Stoll et al., 1990; Bound et al., 1989).

Down syndrome have been reported among infants conceived by **intracytoplasmic sperm injection (ICSI)** (Aboulghar et al., 2001).

OTHER MATERNAL FACTORS

Studies have reported an increased risk for Down syndrome with higher **socioeconomic status**, although the association may be due in part to maternal age (Vrijheid et al., 2000). Parental **education** has not been found to affect Down syndrome risk (Stoll et al., 1990).

Risk of bearing a child with Down syndrome increases with **trisomy in the mother**, **translocation carrier in the parents**, or **previous affected pregnancy in the same sibship** (Uchida, 1970). **Parental mosaicism** is an etiologic factor in recurrent trisomy 21 (Panalos et al., 1992). Increased rates in consanguineous marriages suggest that an **autosomal recessive gene** may predispose toward nondisjunction (Stoll et al., 1990; Alfi et al., 1980). However, a recent investigation reported no statistically significant association between Down syndrome and parental consanguinity (Rittler et al., 2001).

Some evidence suggests that **thyroid disorders in the mother** may increase risk of bearing a Down syndrome child (Hook, 1984; Fialkow et al., 1971). However, other studies found neither **hypothyroidism** nor **hyperthyroidism** to influence risk of Down syndrome (Khoury et al., 1989). Maternal **common cold** with or without fever during the first trimester, **diabetes**, and **epilepsy** do not appear to affect Down syndrome risk (Zhang and Cai, 1993; Stoll et al., 1990).

Families with histories of Alzheimer's disease are more likely to have Down syndrome offspring (NIH, 1985). Of thirteen studies of the association between the two conditions, only four reported a significant relation. However, statistical power may have been lacking in most of them (Schupf et al., 1994).

Mothers of Down syndrome children had more significant **illnesses** before conception, particularly psychological illness, and more **medication ingestion** in the year before conception (Murdoch and Ogston, 1984). These remained statistically significant when adjusted for each other and for maternal age. Unfortunately, specific medications were not identified in this study.

FACTORS IN LIFESTYLE OR ENVIRONMENT

Ionizing radiation is the only known lifestyle/environmental agent to induce nondisjunction in experimental animals (Hook, 1984). Epidemiologic evidence is less conclusive.

- Reports of increased occurrence of chromosomal anomalies from Hiroshima and Nagasaki are not consistent (Awa et al., 1987; Awa, 1975). A similar report from Kerala, India (Kochupillai et al., 1976) has met with criticism (Hook and Porter, 1977).
- Low-dose ionizing radiation from atomic weapon testing correlated with increased occurrence of Down syndrome in a time-series study in England (Bound et al., 1995).
- The Chernobyl reactor accident was presented as an explanation for a cluster of trisomy 21 cases in Berlin (Sperling et al., 1994), though significant clustering at that time was not reported from other European birth defect registries (Harjulehto-Mervaala et al., 1992; de Wals et al., 1988).
- One explanation presented for the increased risk with maternal age is irradiation, such as from x-rays, accumulating over a lifetime (Alberman et al., 1972). However, published data do not confirm x-rays as a risk factor (Evans et al., 1986). Another study reported no association between paternal exposure to ionizing radiation in the nuclear industry and Down syndrome (Doyle et al., 2000).

A statistically significant association was identified with **fathers working in restaurants** at the time of conception (Brender, 1986). Though there were a variety of sanitation violations, no unusual pesticides, cleaning compounds, or use practices were noted. One investigation that examined a variety of **paternal occupations** reported significantly higher rates of Down syndrome with paternal occupation of **janitor**, **mechanic**, and **farm manager/worker** (Olshan et al., 1989), while another study reported no association between paternal occupations of **metal worker**, **sales**, **teacher**, or **agriculture** and rates of Down syndrome (Irgens et al., 2000).

An investigation failed to identify any significant association between Down syndrome and proximity to various types of **industry** (Castilla et al., 2000). Another study found a significant association between proximity to **hazardous waste landfill sites** and risk of chromosomal abnormalities; when the analysis was restricted to Down syndrome, the risk was still elevated, although not statistically significant (Vrijheid et al., 2002). One investigation reported no association between Down syndrome risk and maternal or paternal occupational exposure to **electromagnetic fields**; however, exposure was based on linkage to census data and exposure assessments by an expert panel (Blaasaas et al., 2002).

One study failed to find any link between parental occupational exposure to **lead** and Down syndrome risk. However, the number of cases in the study were small, and the measure of lead exposure was based on census records (Irgens et al., 1998). Maternal use of **contraceptive spermicides** was not found to affect Down syndrome risk (Louik et al., 1987).

A recent investigation reported that risk of a recognized Down syndrome conceptus was reduced with high **alcohol** consumption and high **coffee** consumption. **Smoking** did not appear to affect risk of having a recognized Down syndrome conceptus (Torfs and Christianson, 2000; Van Den Eeden et al., 1990). The authors suggested that high coffee consumption may reduce the viability of a conceptus with Down syndrome so that the conceptus may be lost in early pregnancy.

Studies have reported that women who had infants or fetuses with Down syndrome were more likely to have abnormal **folate metabolism** and **mutations in the methylenetetrahydrofolate reductase (MTHFR) and methionine synthase reductase (MTRR) genes** (O'Leary et al., 2002; Hassold et al., 2001; Hobbs et al., 2000; James et al., 1999). This suggests that periconceptional folic acid supplementation or fortification may reduce Down syndrome risk. However, a study that examined **co-trimoxazole**, a combination of trimethoprim and sulfamethoxazole that is a folic acid antagonist, failed to find any association between the medication and Down syndrome (Czeizel, 1990).

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Please Note: *The primary purpose of this report is to provide background necessary for conducting cluster investigations. It summarizes literature about risk factors associated with this defect. The strengths and limitations of each reference were not critically examined prior to inclusion in this report. Consumers and professionals using this information are advised to consult the references given for more in-depth information.*

This report is for information purposes only and is not intended to diagnose, cure, mitigate, treat, or prevent disease or other conditions and is not intended to provide a determination or assessment of the state of health. Individuals affected by this condition should consult their physician and when appropriate, seek genetic counseling.